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Estimation of loss of quality-adjusted life expectancy (QALE) for patients with operable versus inoperable lung cancer: Adjusting quality-of-life and lead-time bias for utility of surgery

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ABSTRACT

Objectives: This study attempts to quantify the difference in loss of quality-adjusted life expectancy (QALE) for patients with operable and inoperable non-small-cell lung cancer (NSCLC).
Patients and methods: A cohort consisting of 1652 pathologically verified NSCLC patients with performance status 0–1 was monitored for 7 years (2005–2011) to obtain the survival function. This was further extrapolated to lifetime, based on the survival ratios between patients and age- and sex-matched referents simulated from the life tables of the National Vital Statistics of Taiwan. Between 2011 and 2012, EuroQol 5-dimension questionnaires were used to prospectively measure the quality-of-life (QoL) of a 518 consecutive, cross-sectional subsample. We adjusted the lifetime survival function by the utility values of QoL for the cancer cohort to obtain the QALE, while that for the age and sex-matched referents were adjusted to the values collected from the 2009 National Health Interview Survey, and the difference between them was the loss-of-QALE.
Results: The QALE for patients with operable and inoperable NSCLC were 11.66 ± 0.18 and 1.43 ± 0.05 quality-adjusted life year (QALY), with the corresponding loss-of-QALE of 5.25 ± 0.18 and 14.24 ± 0.05 QALY, respectively. The lifetime utility difference for patients with operable and inoperable NSCLC was 9.00 ± 0.18 QALY, after adjustment for QoL and lead-time bias.
Conclusion: The utility gained from surgical operation for operable lung cancer is substantial, even after adjustment for lead-time bias. Future studies should compare screening programs with treatment strategies when carrying out cost-utility assessments to improve patients' values.

1. Introduction

Over the past two decades, the mortality attributed to lung cancer has increased and it is now the leading cause of cancer deaths [1]. Late diagnosis is a fundamental obstacle to improving the outcomes of lung cancer, with more than 70% of new cases presenting too late for curative treatment to be attempted [2]. Owing to the development of new chemotherapeutic agents, the costs of care for inoperable lung cancer are growing rapidly [3]. Therefore, it is worth examining the lifetime utility difference for patients with operable and inoperable lung cancer, which emphasizes the importance of early diagnosis of lung cancer.

For the assessment of lifetime utility difference, both survival and quality-of-life (QoL) should be taken into consideration, and thus, the quality-adjusted life year (QALY) unit is more suitable than estimating survival alone for comparison of various types of healthcare services [4]. Quality-adjusted life expectancy (QALE) can be estimated via adjusting the survival function with the mean QoL at each time point, t, using the following equation [5–7]:

$$\mathrm{QALE} = \int E\left[\mathrm{QoL}\left(t/x\right)\right] S\left(t/x\right) dt$$

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$E[\mathrm{QoL}(t/x)]$ denotes the expected value of health state (QoL) for patients with condition x at time t and $S(t/x)$ denotes the survival function for condition x at time t.

Previous studies discussing the benefits of surgery mostly focused on survival alone, and usually did not take lead-time bias into consideration [8]. Based on a 7-year follow-up cohort, this study aims to quantify the difference in loss-of-QALE for patients with operable and inoperable non-small-cell lung cancer (NSCLC). In other words, we attempt to estimate the utility difference after adjustment for QoL and lead-time bias, which might be regained through future screening initiatives.

2. Patients and methods

The Institutional Review Board of the National Cheng Kung University Hospital (NCKUH) approved the study before commencement (ER-100-079), and every interviewed patient provided written, informed consent. We abstracted a NSCLC cohort from the NCKUH database of lung cancer for survival analysis, applied the national life tables to extrapolate the survival function to lifetime, prospectively collected the QoL data from a cross-sectional subsample of the cohort, and integrated the lifetime survival with the QoL to estimate the QALE and loss-of-QALE of NSCLC patients using the QALY unit.

2.1. The 7-year follow-up cohort for estimation of the survival

All patients with NSCLC and free from other malignancies during the period from January 2005 to December 2011 were recruited from the NCKUH lung cancer database. The diagnosis of NSCLC and its pathological subtypes were based on histology or cytology. We defined the tumor stage of each patient by tumor-node-metastasis classifications [9,10]. Patients with tumor stages I, II, IIIA, and IIIB were assessed by experienced thoracic surgeons for tumor operability. Subjects who underwent pulmonary resections as the curative treatment were recruited as the operable patients, while the others belonged to the inoperable group. The thoracic surgeons decided whether to perform pulmonary resections or not, according to the practice guidelines [11] as well as each patient's pulmonary reserve and co-morbidities. We used the Eastern Cooperative Oncology Group score to classify the performance status of each patient [12]. The score runs from 0 to 5, with 0 denoting fully active and 1–5 denoting restricted in physical strenuous activity, <50% in bed during the day, >50% in bed, bedbound, and dead, respectively. To avoid selection bias in the operable group, only patients with performance status 0–1 were evaluated, however, a sensitivity analysis for subjects with performance status 0–4 was also performed. The survival status for each patient was verified by follow-up from the day of diagnosis till the end of 2011.

2.2. Extrapolating the survival to lifetime

After obtaining the survival function of the cohort through Kaplan–Meier estimate, a method proposed by Huang and Wang was used to extrapolate the survival function beyond the end of the follow-up period [13]. This approach assumed that NSCLC generated a constant excess hazard after the initial follow-up period, and its calculation comprised three steps. First, we borrowed the hazard functions from the life tables of the National Vital Statistics of Taiwan to generate an age- and sex-matched reference population by the Monte Carlo method and estimated its survival function. Second, we calculated the survival ratio between the NSCLC cohort and the reference population at each time t and performed a logit transformation of the ratio. Third, the logit transformations of the ratios were fitted by simple linear regression up to the end of the follow-up period. The estimated regression line, together with survival function of the reference population beyond the follow-up limit, was used to extrapolate the lifetime survival function of the NSCLC cohort. The life expectancy of the NSCLC cohort (up to 600 months) after diagnosis was thus estimated. The expected years of life lost of the NSCLC cohort was defined as the survival difference between the cohort and the reference population. The method described above has been demonstrated by computer simulation [13] and proven mathematically [14]. It has also been corroborated by several examples of cancer cohorts [15,16]. An open access software, the iSQoL statistical package, was used for the computation [17].

2.3. Prospectively measuring the QoL from a cross-sectional subsample

From May 2011 to April 2012, all consecutive patients with NSCLC from the outpatient oncology, chest surgery, and chest medicine departments of NCKUH were invited to participate in this study. To minimize any magnitude of overestimation of the QoL, we also consecutively screened patients admitted to the wards between November 2011 and January 2012. The inclusion criteria were realization of a lung cancer diagnosis by each participant, the absence of malignancy at another site, and each subject's ability to understand and answer the questionnaire. In some individuals, measurements were performed repeatedly; however, each measurement was taken at least 3 months after the previous one.

The 5-dimension EuroQol questionnaire (EQ-5D) [18], the Taiwanese version of which has been validated in a previous work [19], was used with face-to-face interviews to estimate the utility values of QoL. The five dimensions assessed by the EQ-5D are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each of which has three levels of severity. Using the scoring function from Taiwan, these health state parameters were transformed into a utility value ranging from 0 to 1, in which 0 represented death and 1 indicated full health.

The duration-to-date for each measurement was defined as the period between the date of NSCLC diagnosis and the date of interview. A kernel-smoothing (i.e., the moving average of the nearby 10%) method was used to estimate the mean QoL function [6,7]. The utility values of QoL beyond the follow-up period were assumed to be the same as the average of the last 10% of patients near the end of follow-up.

2.4. Estimating the QALE and loss-of-QALE

The lifetime survival function of the NSCLC cohort was adjusted by the corresponding mean QoL function to obtain a quality-adjusted survival curve, in which the sum of the area under this curve was the QALE of NSCLC patients [6]. We borrowed the EQ-5D utility values of the age- and sex-matched general population from the 2009 National Health Interview Survey in Taiwan. After adjusting the utility values with the survival function of the age- and sex-adjusted referents, the loss-of-QALE of NSCLC patients was calculated by subtracting the area under the quality-adjusted survival curve of NSCLC patients from that of the referents. Since the referents were age- and sex-matched with every NSCLC case, the loss-of-QALE would be the expected lifetime utility loss from developing the disease, and the difference between that of operable and inoperable NSCLC patients would be the expected lifetime utility difference after adjustment for lead-time bias.

We further performed a stratified analysis among patients with stage IIIA NSCLC using the above methods. The lifetime utility difference between operable and inoperable stage IIIA patients was also estimated.

2.5. Validating the extrapolation method

To validate the extrapolation method, we used the survival data of patients who were diagnosed during the first 4 years and then extrapolated them to 7 years through the previously described method. Because these patients were actually monitored until the end of 2011, the mean survival duration within the 7-year follow-up, using Kaplan–Meier method, was considered as the gold standard. The relative bias was computed to compare the difference in values between the extrapolation and Kaplan–Meier estimation.

3. Results

A total of 2045 patients visited NCKUH between 2005 and 2011. Individuals with incomplete data ($n = 20$) or no information of performance status ($n = 108$, 5 of them received curative operation) were not included, leaving 1917 patients for this study. Those with performance status 2–4 ($n = 265$, 16 of them received curative operation) were then excluded, and thus the cohort for analysis of survival function consisted of 1652 patients. The prospectively collected cross-sectional subsample for measuring the QoL consisted of 518 participants, and 1147 QoL measurements were performed. Table 1 summarizes the characteristics of patients with operable and inoperable NSCLC for analysis of survival function and measuring the QoL. Operable patients were 1.6 years younger than inoperable patients ($p < 0.05$). The operable subsample for QoL had more male participants than the inoperable subsample ($p = 0.019$). The distributions of tumor stage and comorbidities in each group of patients were also elucidated.

3.1. The QALE and loss-of-QALE

The characteristics of QoL measurements are summarized in Table 2. The utility values of QoL for patients with operable NSCLC were higher than those of inoperable patients. Compared with young-aged patients, old-aged patients had lower utility values of QoL. To obtain the quality-adjusted survival curve (Fig. 1), we multiplied the survival probability by the mean QoL at each time t (duration-to-date). The sum of the shaded area under the curve represents the QALE. Borrowing the utility function of the age- and sex-matched referents from the 2009 National Health Interview Survey in Taiwan, the difference between the area under the quality-adjusted survival curve of the cancer cohort and that of the referents is the loss-of-QALE (Fig. 2). The QALE for patients with operable NSCLC differed significantly from the QALE for patients with inoperable NSCLC, as did the loss-of-QALE for the two groups (Table 2). The difference in loss-of-QALE between operable and inoperable NSCLC patients, or, the net difference after adjustment of potential lead-time bias for age between the two groups, was 9.00 ± 0.18 QALY.

We conducted a sensitivity analysis for patients with performance status 0–4 (Table 2). As patients with performance status more than 2 were usually confined to bed and unavailable to answer the questionnaire, the resulted mean utility values of QoL were similar to those of patients without including them. The difference in QALE between operable and inoperable NSCLC patients would be 10.26 QALY, which was not different from that using patients with performance status 0–1 alone. However, the difference in loss-of-QALE would be underestimated slightly (= 8.36 QALY), probably because of the older mean age of inoperable patients. Another sensitivity analysis was conducted by only including the utility values of the first QoL measurements of 518 patients in the calculations, the difference in QALE would be 10.43 QALY and the difference in loss-of-QALE would be 9.20 QALY for patients with operable and

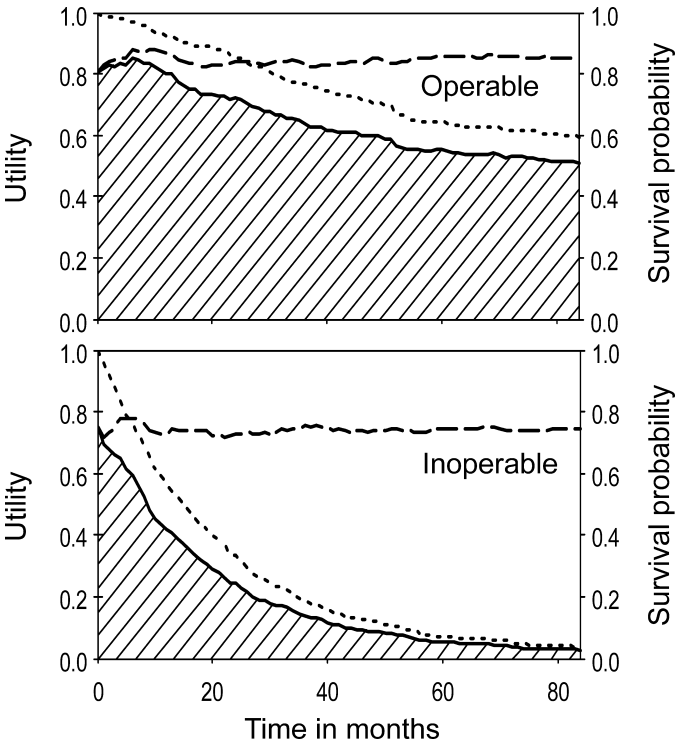

Fig. 1. Quality-adjusted life expectancy (QALE) of patients with operable (upper panel) and inoperable (lower panel) non-small-cell lung cancer (NSCLC). The survival curves (dotted lines), mean utility functions (dashed lines), and quality-adjusted survival curves (solid lines) of patients with NSCLC are shown, and the shaded area represents the QALE.

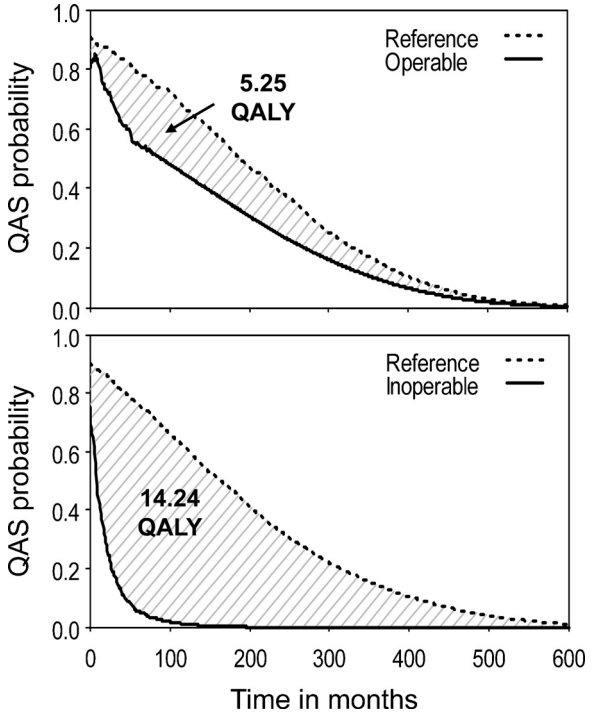

Fig. 2. Quality-adjusted survival (QAS) curves of patients with operable (upper panel) and inoperable (lower panel) non-small-cell lung cancer and the corresponding referents. The shaded area between the QAS curve of patients and that of the corresponding referents is the loss-of-QALE (quality-adjusted life expectancy), which has been adjusted for lead-time bias (Table 2).

Table 1
Clinical characteristics of patients with operable and inoperable non-small-cell lung cancer (NSCLC) for outcome research.

	Operable NSCLC		Inoperable NSCLC	
	Cohort for survival (n = 479)	Subsample for QoL (n = 275)	Cohort for survival (n = 1173)	Subsample for QoL (n = 243)
Age at diagnosis, mean (SD) year	62.9 (10.6)	61.8 (10.2)	64.5 (13.0)	63.4 (11.8)
Male, n (%)	260(54.3)	146(53.1)	683(58.2)	104(42.8)
Performance status				
0, n (%)	328(68.5)	192(69.8)	752(64.1)	168(69.1)
1, n (%)	151(31.5)	83(30.1)	421(35.9)	75(30.9)
Tumor stage				
I, n (%)	258(53.9)	164(59.6)	15(1.3)	2(0.8)
II, n (%)	68(14.2)	40(14.6)	8(0.7)	0(0)
IIIA, n (%)	113(23.6)	49(17.8)	59(5.0)	11(4.5)
IIIB, n (%)	40(8.4)	22(8.0)	218(18.6)	41(16.9)
IV, n (%)	0 (0)	0 (0)	873(74.4)	189(77.8)
Comorbidities[a]				
CVD/neurodegenerative disease, n (%)	12(2.5)	3(1.1)	41(3.5)	9(3.7)
Congestive heart failure, n (%)	6(1.3)	1(0.4)	22(1.9)	5(2.1)
COPD, n (%)	48(10.0)	23(8.4)	91(7.8)	14(5.8)
Cirrhosis of liver, n (%)	3(0.6)	3(1.1)	10(0.9)	0 (0)
End-stage renal disease, n (%)	4(0.8)	4(1.5)	15(1.3)	1(0.4)

Abbreviations: COPD, chronic obstructive pulmonary disease; CVD, cerebrovascular disease; QoL, quality-of-life; SD, standard deviation.
[a] Comorbidities were identified according to the discharge diagnosis prior to the diagnosis of NSCLC.

inoperable NSCLC, and these results are not significantly different from those using repeated measurements.

We also performed a stratified analysis among patients with stage IIIA NSCLC (Fig. 3). Compared with inoperable stage IIIA patients, operable stage IIIA patients had a longer QALE. Moreover, the loss-of-QALE for operable stage IIIA patients was greater than that of inoperable stage IIIA patients, probably because of the younger mean age at diagnosis.

3.2. Validation of the extrapolation

There were 262 patients with operable and 621 patients with inoperable NSCLC diagnosed during the first 4 years, between 2005 and 2008, of which the survival curves were extrapolated to 2011 and compared with the Kaplan–Meier estimates based on the 7-year follow-up. The relative biases of the extrapolation ranged between −4.6% (p = 0.099) and −6.0% (p = 0.116) after 3 years of extrapolation (Table 3).

4. Discussion

Although the QoL for NSCLC patients has been measured previously in several studies [20,21], integrating the survival with utility values of QoL to estimate the lifetime utility difference between patients with operable and inoperable NSCLC has never been comprehensively evaluated. In our study, the utility values of QoL for patients with operable and inoperable NSCLC were stratified into different age bands (Table 2), which show that compared with inoperable patients, operable patients had mean utility values closer to those for the general population (0.96, 0.93, 0.86 for men ≤54 years, 55–74 years, ≥75 years and 0.96, 0.91, 0.78 for women ≤54 years, 55–74 years, ≥75 years, respectively). In addition, we quantified the difference in loss-of-QALE (9.00 ± 0.18 QALY), which was adjusted for QoL and lead-time bias, between patients with operable and inoperable NSCLC. Because we limited the subjects to cases with pathological evidence of NSCLC and monitored them for 7 years, sex- and age-matched them to reference subjects to

Table 2
Results of quality-of-life (QoL) measurements and estimated loss of quality-adjusted life expectancy (QALE).

	Performance status: 0–1		Performance status: 0–4	
	Operable NSCLC (n = 275)	Inoperable NSCLC (n = 243)	Operable NSCLC (n = 281)	Inoperable NSCLC (n = 250)
Number of measurements	634	513	646	528
Time after diagnosis, median (IQR) months	22.1 (11.6–41.5)	12.9 (6.1–25.6)	22.1 (11.4–41.5)	12.9 (6.1–26.1)
Utility value of QoL, mean (SD)				
Male:				
≤54 years	0.86 (0.15)	0.75 (0.24)	0.86 (0.15)	0.75 (0.24)
55–74 years	0.86 (0.16)	0.76 (0.23)	0.86 (0.16)	0.76 (0.23)
≥75 years	0.77 (0.19)	0.67 (0.31)	0.77 (0.19)	0.64 (0.31)
Female:				
≤54 years	0.86 (0.16)	0.79 (0.17)	0.86 (0.16)	0.79 (0.17)
55–74 years	0.82 (0.17)	0.74 (0.22)	0.82 (0.17)	0.74 (0.21)
≥75 years	0.72 (0.23)	0.68 (0.24)	0.72 (0.23)	0.68 (0.24)
Tumor stage:				
I	0.86 (0.17)	–	0.85 (0.17)	–
II	0.83 (0.17)	–	0.83 (0.17)	–
III	0.83 (0.17)	0.73 (0.25)	0.83 (0.16)	0.72 (0.25)
IV	–	0.75 (0.22)	–	0.75 (0.22)
Life expectancy, mean (SE) years	13.69 (0.09)	1.92 (0.06)	13.54 (0.11)	1.65 (0.04)
QALE, mean (SE) QALY	11.66 (0.18)	1.43 (0.05)	11.49 (0.19)	1.23 (0.03)
Expected years of life lost, mean (SE) years	6.83 (0.09)	17.46 (0.06)	6.97 (0.11)	16.99 (0.04)
Loss-of-QALE, mean (SE) QALY	5.25 (0.18)	14.24 (0.05)	5.40 (0.19)	13.76 (0.03)

Abbreviations: IQR, interquartile range; NSCLC, non-small-cell lung cancer; QALY, quality-adjusted life year; SD, standard deviation; SE, standard error.

Table 3
Estimates of mean survival durations for 7 years of follow-up using the extrapolation method based on the first 4 years of follow-up data compared with the Kaplan–Meier estimates based on 7 years of follow-up data.

	Cohort size	7-Year follow-up Kaplan–Meier estimate, mean (SE) months	Estimate using the extrapolation based on the first 4 years of follow-up, mean (SE) months	Relative bias, %	*p* value
Operable	262	63.3 (1.6)	60.4 (0.8)	−4.6	0.099
Inoperable	621	21.7 (0.7)	20.4 (0.6)	−6.0	0.116

Abbreviation: SE, standard error.

estimate life expectancy, and adjusted for the utility values of QoL of an actual cohort and the corresponding referents in a real-world setting, our estimations were not confound by the preceding factors. Additionally, validation of our extrapolation method showed that the relative biases are small after 3 years of extrapolation. We thus tentatively conclude that such estimations would be useful for lifetime utility analysis of cancer under different treatments, and detection of NSCLC patients at the operable stage would save more than 9 QALY. Moreover, operable IIIA patients were found to have a greater loss-of-QALE than inoperable IIIA patients (Fig. 3), which might imply a controversy in current practice. Since the sample size in the current study is relatively small, we recommend that future works matched on propensity scores be conducted to corroborate our results for potential reconsideration of clinical practice guidelines.

We selected patients with performance status 0–1 to estimate the differences in survival, QoL, and QALE. As patients with performance status 2–4 were usually confined to bed and physically unsuitable for curative operation, including them into the study might result in selection bias. Besides, most of them were unable to answer the questionnaire, thus the mean utility values would be overestimated. A sensitivity analysis including all subjects with performance status 0–4 (Table 2) was conducted and corroborated

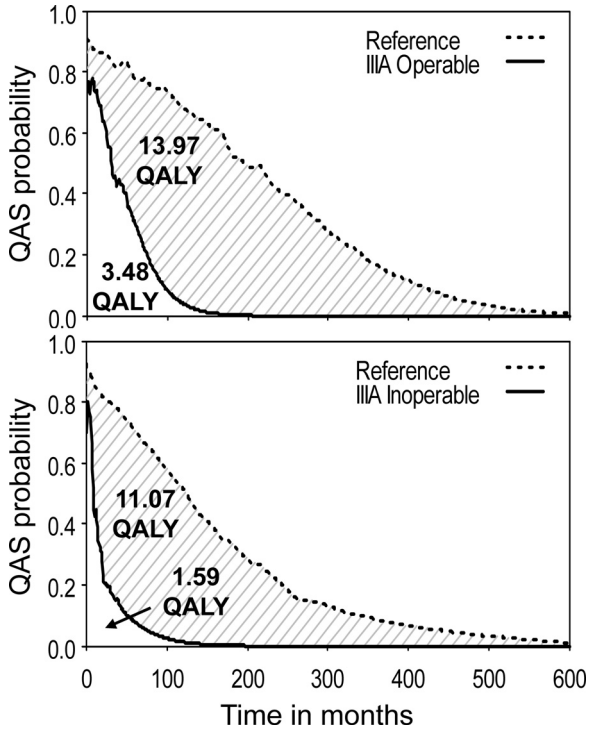

Fig. 3. Quality-adjusted life expectancy (QALE) and loss-of-QALE of patients with operable (upper panel) and inoperable (lower panel) stage IIIA non-small-cell lung cancer. The quality-adjusted survival (QAS) curves of patients (solid lines) and the corresponding referents (dotted lines) are shown. The blank area represents the QALE, whereas the shaded area represents the loss-of-QALE.

our conjectures. The mean utility values for patients with performance status 0–4 were almost the same to those of patients with performance status 0–1, while the difference in loss-of-QALE was slightly underestimated because the mean age of the inoperable group became older and their loss of life expectancy became smaller.

Unlike previous studies that applied internationally chosen life tables together with the experts' determination of disability weights to calculate the disease burden of lung cancer using disability-adjusted life year (DALY) [22,23], we applied the national life tables of Taiwan and a cross-sectional sample of patients for measurement of QoL to estimate the QALE and loss-of-QALE by using QALY as the unit. While the DALY method makes international comparisons more feasible, the loss-of-QALE allows direct comparisons of different diagnosis and treatment strategies, and would likely be more useful for making decisions regarding the cost-effectiveness of national health policies.

In our cohort, the 5-year survival rates for different stages of NSCLC (79.9%, 44.1%, 20.2%, and 7.7%, respectively, for stages I, II, IIIA, and IIIB-IV NSCLC) appeared comparable to those demonstrated by the National Cancer Institute [24]. However, the utility values of NSCLC patients in our cross-sectional subsample were higher than those reported in other studies [20,21], which may be attributed to several reasons. First, all patients must have performance status 0–1 to be included for analysis and most (86.1%, 446 of 518 patients) of our subjects were recruited from outpatient departments. They were thus less likely to have any severe adverse effects and would have higher utility values [20]. Second, because insight into the diagnosis of lung cancer was one of the inclusion criteria required by the Institutional Review Board, the utility values of our patients would usually be higher [25]. Third, we assumed that patients remained at the same level of QoL near the end of the follow-up period while extrapolating the QoL function to lifetime. Such an assumption could result in a higher QoL value, because the actual utility value usually declines with age [26]. However, as the life span of lung cancer patients is short and both groups of patients were treated in the same way, the difference between them would not be confounded by this approach.

Several limitations must be acknowledged in this study. First, since we used an age- and sex-matched reference population instead of patients with the same comorbidities, the QoL and survival of our patients might be affected by major chronic diseases. Fortunately, Table 1 shows minor differences in the prevalence rates for the two comparison groups and corresponding cross-sectional subsamples. We further limited the recruitment to those with performance status 0–1 and free from other malignancies, thus the results would not be biased too much. Second, QoL measurements from some individuals were performed repeatedly. Nevertheless, as each measurement was taken at least 3 months apart and the results using repeated measurements did not differ from those only including the first QoL measurements, the potential bias would be minimal. Third, the estimation of QALE would have been more accurate if we had measured the QoL of every patient in the cohort repeatedly during the follow-up period. Unfortunately, we were unable to conduct such a study, and thus used a

consecutive, cross-sectional subsample of patients who were healthy enough to accept our invitations for interviews.

5. Conclusion

In conclusion, we successfully estimated the QALE and loss-of-QALE of operable and inoperable NSCLC patients. The lifetime utility gain from surgical operation is 9 QALY after adjusting for QoL and lead-time bias. Future studies may focus on comparing screening programs with treatment strategies to obtain the cost-per-life year and/or cost-per-QALY for technology assessment and possible development of cost-effective clinical guidelines.

Conflict of interest statement

The authors declare that they have no competing interests.

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